

GAO

Report to the Ranking Minority
Member, Subcommittee on Public
Health, Committee on Health,
Education, Labor, and Pensions,
U.S. Senate

November 2001

BIOMEDICAL RESEARCH

HHS Direction Needed to Address Financial Conflicts of Interest

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Abbreviations

AAMC	Association of American Medical Colleges
AAU	Association of American Universities
AIDS	acquired immunodeficiency syndrome
AUTM	Association of University Technology Managers
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IRB	institutional review board
NHRPAC	National Human Research Protections Advisory Committee
NIH	National Institutes of Health
OER	Office of Extramural Research
OHRP	Office for Human Research Protections
PHS	Public Health Service



United States General Accounting Office
Washington, DC 20548

November 26, 2001

The Honorable Bill Frist
Ranking Minority Member
Subcommittee on Public Health
Committee on Health, Education, Labor, and Pensions
United States Senate

Dear Senator Frist:

Recent allegations that conflicts of interest may have affected the integrity of biomedical research and led to harming human research subjects have heightened concerns about the financial relationships between individual research investigators or their research institutions and private industry. The Bayh-Dole Act, enacted in 1980, facilitated research collaborations between private industry and research institutions such as universities, and since then, financial relationships between them have grown.¹ In biomedical research, these relationships often pair academic research expertise and facilities with industry resources for technology transfer in order to bring innovations from the laboratory into practical medical application. The increase in financial collaborations has paralleled 2 decades of rapid growth in federal and private biomedical research spending, now reaching into the billions of dollars each year.² These financial partnerships and research funding have yielded significant achievements, notably treatments for diseases and conditions such as acquired immunodeficiency syndrome (AIDS) and strokes.

Their benefits notwithstanding, some collaborations have raised concerns that research investigators or institutions that have significant financial interests in the research may focus attention on the financial rewards of the research, compromising its integrity and the safety of human subjects. In such situations, the significant financial interest presents a conflict of interest.

¹Amendments to the Patent and Trademark Act, P.L. 96-517 § 6(a), Dec. 12, 1980, 35 U.S.C. §§ 200-212. Section 6(a) is commonly referred to as "Bayh-Dole" after its two main sponsors, former Senators Birch Bayh and Robert Dole.

²The federal government funds biomedical research primarily through the Department of Health and Human Services' (HHS) Public Health Service with grants from the National Institutes of Health. Nongovernment (private) funding comes from sources such as drug or biotechnology companies.

HHS regulations pertaining to financial interests in biomedical research are divided into rules covering federally funded research and rules governing privately funded, federally regulated research. For HHS-funded research, institutions receiving grants from the National Institutes of Health (NIH) must abide by a Public Health Service (PHS) regulation governing individual investigators' financial interests.³ Sponsors of publicly or privately funded research on drugs, medical devices, or biological products, such as vaccines, regulated by the Food and Drug Administration (FDA) must abide by FDA's regulation concerning investigators' financial interests when filing a marketing application.⁴ (See app. I for a description of federal regulations pertaining to the financial interests of research investigators.) While these regulations govern the financial interests of individual investigators, no similar federal regulations apply to the financial interests of an institution.

HHS' Office for Human Research Protections (OHRP) plays a role in enforcing the HHS financial interest regulations through its oversight of institutional review boards (IRB), which review research involving human research subjects.⁵ OHRP, which oversees all research conducted or funded by HHS that involves human subjects, is responsible for enforcing the HHS human subjects protection regulations.⁶

Because of your concerns about the risks that financial conflicts of interest pose to the integrity of biomedical research and the well-being of human research subjects, you asked us to examine (1) how academic research institutions are implementing HHS' regulations governing

³PHS, an operating division within HHS, includes agencies such as NIH, the Centers for Disease Control and Prevention, and the Food and Drug Administration; and program offices under the Office of Public Health and Science such as the Surgeon General, Emergency Preparedness, and Minority Health.

⁴A sponsor is defined as the party that supports a particular study at the time it was carried out. (21 C.F.R. § 54.2 (h)). Marketing applications are often filed by sponsors, but in some cases applicants may contract out for covered studies.

⁵Institutions conducting research using human subjects must have their IRBs review and approve research proposals. Usually, the majority of IRB members are affiliated with the institution. Some institutions rely on commercial or independent IRBs.

⁶The human subjects protection regulations (45 C.F.R. pt. 46) are a set of requirements embodied in regulation for the protection of human research subjects; they apply only to HHS funded or HHS sponsored research. FDA has comparable regulations for FDA regulated research (21 C.F.R. pts. 50, 56). Other federal agencies involved in human subjects research have similar regulations.

individual investigators' financial interests, (2) the types of policies and procedures these institutions have to minimize and manage institutional financial conflicts of interest, and (3) the HHS regulations and oversight intended to ensure that financial conflicts of interest do not affect the integrity of research and the safety of human research subjects.

To address these objectives, we reviewed the HHS regulations on research investigators' financial interests and the protection of human research subjects; interviewed officials at NIH, FDA, OHRP, and experts at academic associations (including the Association of American Medical Colleges and the Association of American Universities) and other relevant organizations (including the National Bioethics Advisory Commission); and visited five universities to study in-depth their financial conflict-of-interest policies and processes.⁷ We selected these universities from among the 20 institutions that receive the largest funding from NIH for biomedical research and that have a high degree of technology transfer activity (that is, the patenting and licensing of new technologies). Although our focus was financial conflicts of interest in biomedical research, at each university, we reviewed universitywide policies and procedures on financial conflicts of interest and related matters and interviewed administrative officials. We also interviewed biomedical research investigators, and we reviewed a sample of financial disclosure files of biomedical research investigators. Because we looked at a relatively small sample of the 483 institutions of higher education receiving research funding from NIH in fiscal year 1999, our findings are not generalizable to other universities or nonacademic research institutions. We performed our work from February through September 2001 in accordance with generally accepted government auditing standards. (App. II describes our scope and methodology in greater detail.)

Results in Brief

The five universities in our study had developed broad policies and procedures regarding individual investigators' financial conflicts of interest as required by the PHS regulation that, for the most part, applied to both publicly and privately funded research. Federal requirements on disclosure of financial interests and management of conflicts of interest are flexible to allow institutions to implement them in ways that meet their

⁷The five universities are the University of California, Los Angeles; University of North Carolina, Chapel Hill; University of Washington, Seattle; Washington University, St. Louis; and Yale University, New Haven.

individual circumstances. Consequently, the universities' policies differed in their content, such as the kinds of financial relationships they considered to be manageable conflicts of interest, and in their implementation. In addition, although they all used similar management strategies for conflicts, they differed in how they employed them. The data for overseeing various aspects of investigators' research activities and financial interests were kept in multiple offices, files, and formats within each of the five universities, making it a challenge to ensure that conflicts of interest were appropriately managed and not overlooked. All five universities had difficulty providing basic data on investigators' financial conflicts of interest in clinical research involving human subjects. The universities generally acknowledged a need for better coordination of information about investigators' financial relationships, and several of the universities told us they were developing mechanisms to do so. University officials said they would like to have access to information from HHS and other institutions about institutions' policies and implementation practices, which could help them improve their practices.

Policies and procedures at the five universities addressed aspects of institutional financial conflicts of interest, such as technology transfer activities and financial relationships with small start-up companies that market university-developed products. For example, they established a "firewall" between the overall management of the institutions' investments and their academic affairs, including research activities, thereby encouraging independent decisionmaking in each area. Policies and procedures in the areas of technology transfer and university-related start-up companies varied considerably. Two of the five universities, for example, separated their technology transfer offices organizationally from other research activities, which officials said helped keep ongoing research from affecting revenue-generating decisions. In addition, the universities placed limits on the amount of their equity holdings—ranging from 2 percent of a company's equity at one university to 49 percent at another—and on their roles in the management of university-related start-up companies.

The HHS regulations and its oversight of financial conflicts of interest in biomedical research have limitations for promoting the integrity of research and protecting human subjects. First, the HHS financial interest regulations—both the PHS and FDA regulations—are not directly linked to the regulations on human subjects protection, which means that financial interest information may not necessarily be conveyed to IRBs for consideration when they review research proposals for risks to human subjects. Second, the PHS and FDA financial interest regulations differ in

terms of when they require review of investigators' financial disclosures, and in the amounts of their disclosure thresholds. Institutions are required to report investigators' financial conflicts of interest to PHS before research funds are spent; FDA is not involved in reviewing financial disclosures until a sponsor submits that information as part of a marketing application, which is after the research has been completed. Third, although the PHS regulation does not require institutions to report the specific details of a financial conflict of interest, some of the universities we visited were still confused about the conditions under which they needed to report and what they needed to report. One university, for example, mistakenly assumed it needed to report only the financial conflicts of interest that could not be managed; therefore, if it had eliminated a conflict of interest, it did not report it. Recently, HHS has taken steps to improve its oversight and monitoring. NIH has included a review of financial conflict-of-interest issues in its site visits to institutions, and FDA now lists the review of financial disclosures in its guidance to reviewers of drug marketing applications. In addition, HHS has drafted guidance on financial conflicts of interest that is promising. However, this guidance does not provide detailed advice on managing institutional financial conflicts of interest.

We are recommending that HHS undertake efforts to highlight and communicate best practices for institutions to identify and manage investigator and institutional financial conflicts of interest. We are also recommending that HHS develop specific guidance or regulations to address institutional financial conflicts of interest. In its comments on a draft of this report, HHS concurred with our recommendations.

Background

Enormous growth in government and private biomedical research funding and in financial relationships between government-funded investigators and private industry has increased the potential for financial conflicts of interest to occur that could compromise research integrity and the safety of participants. HHS has regulations on individual investigator financial interests in federally funded or regulated research. The academic and professional communities also have developed policies and guidelines on conflicts of interest and have recently devoted resources to study this issue in more depth.

Growth in Biomedical Research Funding and Collaborative Relationships

The budget of NIH, the principal federal agency that funds biomedical research, grew from a little over \$3 billion in fiscal year 1980 to more than \$20 billion in fiscal year 2001. Most NIH grants and contracts are awarded through universities and medical centers to investigators conducting research at these institutions. Private industry funding grew even more rapidly—funding by drug companies alone rose from \$1.5 billion in 1980 to \$22.4 billion in 2000.⁸ Industry sponsors of biomedical research either conduct the research themselves or provide the funding to university investigators, other research institutions, contract research organizations, or private medical practices. Collaborations between government-funded research investigators and private industry also have increased, in part because of the Bayh-Dole Act. The act gave universities, nonprofit corporations, and small businesses the ability to retain patents and commercialize their federally funded inventions in order to facilitate the commercialization of new technologies. University-generated patents rose from about 250 per year before 1980 to more than 4,800 in 1998.

Investigator and Institutional Financial Conflicts of Interest

As the boundary between academia and industry has become less distinct, concerns have been raised about the potential for financial conflicts of interest in investigators' as well as institutions' relationships with private industry. Investigators' financial relationships with outside interests can include working, contracting, or consulting for a company; holding a management position or board membership or having other fiduciary relationships; or owning stock or other securities. A conflict of interest occurs when these relationships compromise, or appear to compromise, an investigator's professional judgment and independence in the design, conduct, or publication of his or her research. For example, financial conflicts of interest may affect the recruitment of human research subjects such that inappropriate participants are enrolled. These conflicts also may influence the informed consent process—by which the risks and benefits of a study are communicated to the participants—resulting in participants who are not fully informed about a study's potential harm to them. Furthermore, an investigator's financial stake in a product may bias the development and reporting of research results or make the investigator reluctant to share information with other investigators in order to maintain his or her competitive edge. Financial conflicts of interest could bias the publication of research findings. For example, a corporate sponsor of research with a vested financial interest in the study outcome

⁸PhRMA, Pharmaceutical Industry Profile 2000.

may try to ensure that only findings favorable to the sponsor's product are published.

Institutional financial conflicts of interest may arise because of an institution's desire to participate in technology transfer activities and its need to remain financially sound. While companies may invest in universities by supporting positions such as endowed chairs or facilities such as research laboratories, universities also may invest financial resources in companies that sponsor research at the institution. Such investments would include owning stock in a pharmaceutical company or investing in a small start-up company formed by entrepreneurial faculty who have invented products and want to market them commercially. Start-up companies are generally nonpublicly traded enterprises. An investor's financial stake in a start-up may result in future financial gain. Sometimes, however, an institution's economic goals may conflict with its goals of fostering objective, unbiased research. Financial interests may color its review, approval, or monitoring of research conducted under its auspices or its allocation of equipment, facilities, and staff for research. For example, in a case that came to light in the late 1980s, the president of one large university provided venture capital equal to one-fifth of the university's endowment (funds that support the university) to invest in a biotechnology start-up company that used technologies the university developed, with the university consequently holding more than 70 percent of the company's equity. The company also had university officials on its board of directors and conducted research through the university. Because of these ties, university decisions about research were inappropriately commingled with financial decisions about the start-up company.

Federal Oversight and Regulations

Within HHS, responsibility for the oversight of federally funded or regulated biomedical research rests primarily with three entities: NIH, FDA, and OHRP. NIH is charged with ensuring that the research it funds complies with applicable HHS regulations, including a PHS regulation on individual investigators' financial interests.⁹ This regulation, promulgated in 1995, requires PHS-funded organizations or institutions (which include all NIH-funded organizations) to maintain and enforce written policies on financial conflicts of interest; inform their investigators of these policies; and require investigators to disclose any "significant financial interests" in

⁹42 C.F.R. pt. 50 Subpart F.

entities whose financial interests may be affected by the research. While the PHS regulation uses the phrase "conflict of interest" without defining it, the regulation defines a "significant financial interest" as including income of an investigator or investigator's spouse or dependent child expected to exceed \$10,000 over 12 months, or equity interests exceeding \$10,000 or 5 percent ownership of a company. It is left to institutional officials to determine which significant financial interests constitute conflicts of interest. Institutions must report a financial conflict of interest to the PHS awarding component and explain whether the conflict has been "managed, reduced, or eliminated." The PHS regulation does not define these terms but provides several examples of strategies to be used. In practice, the management of a financial conflict of interest includes strategies to monitor any effects as well as to reduce or eliminate the financial interest.

FDA is responsible for ensuring that the financial interests and arrangements of clinical investigators do not interfere with the reliability of data submitted to FDA in support of marketing applications for drugs, biological products, or medical devices. Under FDA's financial interest regulation,¹⁰ effective in 1999, sponsors submitting marketing applications must certify that investigators did not have certain financial interests and arrangements, or must disclose them. FDA uses this information in conjunction with information submitted on the design and purpose of the study, and information obtained through on-site inspections, to assess data reliability. In contrast to PHS, FDA's thresholds for financial interests requiring disclosure include payments made by the sponsor of a study to the investigator or his or her institution exceeding \$25,000 (beyond the costs incurred in conducting the study) or any equity interest an investigator has in a publicly held company sponsoring the research that exceeds \$50,000.

OHRP oversees all research conducted or funded by HHS that involves human research subjects¹¹ and enforces the HHS regulations regarding the protection of human subjects.¹² HHS' human subjects protection

¹⁰Principally, 21 C.F.R. pt. 54, and applicable portions of parts 312, 314, 320, 330, 601, 807, 812, 814, and 860.

¹¹OHRP is in the Office of the Assistant Secretary for Health. HHS established OHRP in June 2000 to assume the human subject protection functions of the former Office for Protection From Research Risks, which was part of NIH.

¹²45 C.F.R. pt. 46.

regulations do not address directly the disclosure and management of investigators' financial conflicts of interest. However, the regulations do require a university's IRB, which reviews research proposals involving human research subjects, to weigh a study's risks and benefits to participants, and review the study's participant consent form, as part of its review of the research. Because financial conflicts of interest may affect the risk-benefit analysis, the purpose of the IRB review implies consideration of them. While the actual IRB review of a research proposal may not explicitly consider financial conflicts of interest, IRBs have the right to request and review information about investigators' financial interests that might pose risks to subjects, and they may require an investigator to disclose significant financial interests to the research subjects in the consent form. The human subjects protection regulations also state that an IRB member may not participate in the initial or continuing review of any project in which he or she has a conflicting interest, except to provide information requested by the IRB.¹³

Unless biomedical research is federally funded or involves research or products that need federal approval, it is not necessarily subject to the HHS regulations and oversight pertaining to financial interests and human subjects protection. A significant and growing amount of privately funded biomedical research exists that is not under the purview of HHS regulations and oversight.

Policy and Guidance From Associations and Medical Journals

The academic community and professional associations have demonstrated concern about financial conflicts of interest in biomedical research for a number of years and have taken steps to address this issue. In 1990, the Association of American Medical Colleges (AAMC) issued a document that in part defined institutional and individual responsibilities for dealing with conflicts of interest in research and provided guidance to institutions in developing policies and procedures to meet their unique situations and local requirements.¹⁴ In 1993, the Association of American Universities (AAU) developed a framework for managing investigators' financial conflicts of interest.¹⁵ Also in 1993, the Association of Academic

¹³45 C.F.R. § 46.107 (e), 21 C.F.R. § 56.107 (e).

¹⁴See *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research* (Washington, D.C.: AAMC, 1990).

¹⁵See *Association of American Universities Framework Document on Managing Financial Conflicts of Interest* (<http://www.aau.edu/reports/FrwkCOI.html>).

Health Centers convened a task force to study institutional financial conflicts of interest and their management. Although this task force produced a report, it did not develop specific guidelines on institutional financial conflicts of interest.¹⁶

More activity has occurred recently, partly because of concerns about reports that financial conflicts of interest were associated with harm to research participants. In April 2000, the American Society of Gene Therapy adopted a policy strongly encouraging that its members have no equity, stock options, or comparable arrangements in companies sponsoring a clinical trial. Also in 2000, AAU formed the Task Force on Research Accountability, which issued a report in June on improving the management of human subjects protection systems.¹⁷ In October 2001, the Task Force issued a report on the management of individual and institutional financial conflicts of interest, with specific guidelines and recommendations.¹⁸ In 2001, AAMC convened a task force of clinical investigators; patient representatives; medical school, teaching hospital, and university leaders; and representatives from industry, the legal community, and the media to study the issue of conflicts of interest, update AAMC's 1990 guidelines, and develop new principles for addressing institutional financial conflicts of interest.

Editors of the major medical journals also have expressed concern about the competitive economic environment in which some clinical research is conceived, study subjects are recruited, and data are analyzed and reported. In response to these concerns, the International Committee of Medical Journal Editors has revised and strengthened the section on publication ethics in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication*, which is a reference widely used by individual journals as a basis for their editorial policies.¹⁹ As part of the document's revised reporting requirements, authors will need to disclose details of their own and the

¹⁶See *Conflicts of Interest in Institutional Decision-Making* (Washington, D.C.: Association of Academic Health Centers Task Force on Science Policy, 1994).

¹⁷See *Report on University Protections of Human Beings Who Are the Subjects of Research* (Washington, D.C.: AAU, 2000).

¹⁸See *Report on Individual and Institutional Financial Conflict of Interest* (Washington, D.C.: AAU, 2001).

¹⁹See Frank Davidoff and others, "Sponsorship, Authorship, and Accountability," *New England Journal of Medicine*, Vol. 345, No. 11 (2001), pp. 825-6.

sponsor's role in a study. Some journals also may require the primary authors to sign statements that they accept full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish.

Universities Developed Broad Conflict-of-Interest Policies for Investigators That Varied in Implementation

The five universities we visited developed written financial conflict-of-interest policies for individual investigators that, for the most part, extended to all publicly and privately funded research but varied in their content and in how they were implemented. For example, the universities differed in the kinds of financial relationships—such as paid consulting and holding equity in a company—they considered to be manageable conflicts of interest. In addition, some universities used formal monitoring committees to manage conflicts, while one university allowed investigators to develop self-management plans. The universities generally allowed investigators to self-certify compliance with financial conflict-of-interest policies. Administrative data used to oversee investigators' research activities and financial relationships at all five universities were kept in various offices and in different databases. The universities generally acknowledged a need for better coordination, and several of the universities told us they were taking steps to develop these linkages. Officials at some of the universities told us that they would like to have access to information from HHS and other institutions that could help them improve their practices.

Universities' Conflict-of-Interest Policies Predated and Extended More Broadly Than Federal Requirements

The written financial conflict-of-interest policies at four of the universities we visited extended beyond the requirements of the PHS financial interest regulation to apply to all research conducted at the universities, whether it was funded publicly or privately. The fifth university's written policy covered all publicly and privately funded research except research sponsored by certain foundations and other nonprofit organizations. Concern about actual, potential, or even perceived conflicts of interest has led many other research institutions to develop financial conflict-of-interest policies that are broader than what the federal regulation covers. A recently published survey of the top 100 NIH-funded research institutions reported that more than 70 percent of the 89 respondents had written policies that were more extensive than the federal regulation.²⁰

²⁰Mildred Cho and others, "Policies on Faculty Conflicts of Interest at U.S. Universities," *Journal of the American Medical Association*, Vol. 284 (2000), pp. 2203-8.

Four universities we visited had policies that predated the PHS regulation, and they revised these policies following the regulation's implementation in 1995. The fifth university developed its policy the year that PHS published its regulation. In part because of the recent focus on conflict-of-interest issues, four of the five universities were in the process of reviewing and revising their policies and procedures. These four universities had formed task forces or working groups to assess their policies and procedures and adapt them to the changing research environment.

Universities Varied in Financial Conflict-of-Interest Policies and Management but Generally Allowed Investigators to Self-Certify Compliance

The PHS regulation is flexible to allow institutions to implement it in ways that meet their individual circumstances. The five universities had differences in threshold amounts, timetables for disclosure, and processes for disclosure. And, although they all used similar strategies to manage financial conflicts of interest, they differed in how they employed them. The extent of IRB involvement in the review of financial conflicts of interest also varied, ranging from reviewing investigators' financial disclosure documents to obtaining verbal information from investigators and relying on informal exchanges between its members and the conflict-of-interest committee. All five universities, however, generally relied on investigators to monitor their own compliance with the schools' financial conflict-of-interest rules.

Policies and Procedures

In addition to being shaped by the federal requirements, institutions' policies and procedures also may reflect state laws, court cases, the institution's experiences with financial conflicts, its organizational structure, and its technology transfer activity. For example, state ethics laws influenced the policies at two universities we visited, and a court case also influenced one of these universities' policies.²¹ Four of the universities had written policies with categories and classifications of financial conflicts of interest. However, the fifth university's written policy did not have fixed rules about potential financial conflicts of interest but instead listed 13 specific examples of activities that represented actual, possible, or no conflict of interest.

²¹As a result of this court case, the university was required to disclose investigators' possible financial conflicts of interest in the consent form when study participants were informed about the risks and benefits of a study.

Policies at the five universities required research investigators to disclose to the institution any significant financial interests. Three universities set the threshold for disclosure at the same level as the PHS requirement. Another set the threshold for publicly sponsored research at the PHS level, while, for privately sponsored research, it set a separate threshold of \$250 in income or holdings. The remaining university set the overall threshold for disclosure at the PHS level but had a more stringent disclosure policy for investigators involved in clinical trials. To help protect the interests of human research subjects, this university required an investigator doing clinical research who has any financial interest in the study to disclose it to the institution. Officials at one of the other universities told us they also are considering whether to lower their threshold from the PHS level for disclosure of financial interests in clinical research. At four of the five universities, the overall proportion of clinical researchers who disclosed a significant financial relationship averaged 5 percent. At one university, these data were not readily available.

The five universities differed in their timelines and processes for disclosure of significant financial interests. Three of the universities required an annual disclosure by research investigators, and two required disclosure when a research proposal was submitted. All required updates whenever there was a change in the investigator's financial interests. Their disclosure forms also varied, ranging from simply asking whether a significant financial interest exists and what type of interest it is to asking detailed questions about the nature and amount of the financial interest. Several disclosure forms required supporting information to be provided as an attachment or to be submitted later. All of the universities took steps to preserve the confidentiality of personal information, with some taking stronger measures than others. For example, while all five limited review of disclosure forms to university officials or a designated committee, one university redacted the names of investigators in the disclosure forms before giving them to the conflict-of-interest committee for review.

All five of the universities in our study had conflict-of-interest committees that were responsible for the development and implementation of financial conflict-of-interest policies and procedures. The configuration of these committees and the extent of their involvement in the review of disclosures varied. All five universities had universitywide committees that handled the review of financial conflicts of interest. Three of these universities had additional medical school conflict-of-interest committees. At two of the five universities, either the chairperson of, or staff to, the committee reviewed all disclosure forms and determined whether the financial interest was a conflict, which would then need to be managed,

reduced, or eliminated; they referred complex cases to the full committee for discussion and action. At another university, each department chairperson reviewed the department's investigator disclosures and forwarded disclosures of activities that may be allowable or are presumptively not allowable to the committee for further review. At the other two universities, the committee members reviewed each financial disclosure.

We found some variation among the five universities in how their conflict-of-interest committees evaluated significant financial relationships. The committees make these determinations in response to the PHS regulation, which requires universities to decide whether a disclosed relationship constitutes a financial conflict of interest that needs to be managed, reduced, or eliminated. For example, one school's policy stated that an investigator conducting clinical research on a product he or she developed that was licensed to an external organization in which the investigator had equity or other direct relations might be permitted to continue with the research after disclosure, with appropriate safeguards in place. But another university's policy stated that such a relationship would present serious problems and that it would consider the relationship inappropriate unless it could be managed very closely. In addition, while one university typically allowed investigators who received grant funding to hold equity or receive consulting fees from a company for which they were conducting clinical research, another university strongly discouraged or limited this practice.

IRB involvement in the review of financial conflicts of interest also varied at the five universities we visited. University officials told us that IRB members, following federal regulations, recused themselves from reviewing research protocols when they had a conflicting interest. At some of the universities, the IRBs were more aware of investigators' financial interests than at others. The IRB members at one university reviewed faculty financial disclosure forms in detail as part of their review of the research protocol, checked to make sure that all investigators associated with the grant had filed disclosure forms, and, when appropriate, required disclosure to human research subjects. At three other universities, the conflict-of-interest committee was supposed to send the IRB a memo or report that summarized the financial conflict and recommended a management strategy. At two of these three universities, the IRB could overrule the management strategy the conflict-of-interest committee recommended. At the third university, the IRB did not have the authority to overrule a management strategy. The IRB at the remaining university had no formal communication with the conflict-of-interest committee;

instead, IRB members obtained verbal information about financial interests from investigators. Officials at this university told us they also relied on the overlapping membership between the conflict-of-interest committee and the IRB to surface any issues regarding investigators' financial conflicts of interest.

Management Strategies

The universities we visited did one or more of the following to manage financial conflicts of interest: (1) required disclosure, (2) monitored the research, and (3) required divestiture of the financial interest. The application of these strategies differed, however. Some universities had fairly formal guidelines about when each strategy should be used, while others applied the strategies on a case-by-case basis. For example, officials at one university told us that the strategy used was sometimes determined through negotiation and cooperation between the investigator and the conflict-of-interest committee.

Disclosure of the financial interest can take different forms, depending on the institution. One of the five universities we visited required all investigators who reported financial interests to the institution to disclose them in publications. The four remaining universities did not have an across-the-board policy to require investigators to disclose financial interests in publications, and some of the four decided on a case-by-case basis. At two universities, if human research subjects were involved, investigators had to disclose the interests to their study subjects. One of these two universities required investigators to use specific language in the consent form that described the investigator's financial relationship with the study sponsor. The other three universities decided on a case-by-case basis whether investigators would be required to disclose financial interests in the consent form.

Monitoring the research can involve establishing a formal monitoring committee consisting of several faculty members who meet with the investigator periodically to make sure that the significant financial relationship is being handled appropriately and is not harming the integrity of the research. For example, at one university, a subcommittee of the medical school conflict-of-interest committee develops a "monitoring plan" for each case, outlining the composition, appointment, and responsibilities of the monitoring committee. The plans are contingent upon approval from the universitywide committee, and the subcommittee ensures that the plan is carried out. Conversely, monitoring can be informal and involve, for instance, an investigator designing a personal "self-management" monitoring plan that satisfies the university's requirement for managing the financial conflict of interest. For example, at

one university, an investigator with a significant financial interest in a company designed a self-management monitoring plan that included limiting the time spent with the company, keeping track of the time spent with this company, and not allowing the company to be involved with the research laboratory.

Divestiture of the financial interest is also an option, but several universities told us that this strategy is infrequently imposed on investigators and not often chosen by them. Of 111 investigators at four of the universities we visited who had significant financial relationships with industry in 2000, only 3 voluntarily divested their interests; none were told to divest by their universities.²² Some investigators with significant financial interests may decide not to be involved in conducting the study, but if they are the only ones with a key skill or knowledge for a particular study, they may still want to play a role. For instance, an investigator in a privately funded study at one university we visited was willing to relinquish her rights as the head investigator on the project involving a new surgical procedure but insisted that she be present in the operating room during the surgery because of her expertise and understanding of the procedure. Subsequently, the informed consent form was altered to reveal the investigator's financial interests; other investigator-initiated safeguards, such as disclosure in publications of the investigator's financial interest, were put into place; and the investigator was permitted to be present during the surgery.

Compliance Enforcement

Each of the five universities' written conflict-of-interest policies stated that an investigator's failure to comply with the policy, such as not disclosing a significant financial interest or not following the required management strategy, is cause for disciplinary action, ranging from fines to termination of employment. University officials told us that they rarely determined that sanctions were warranted. None of the five universities had formal processes for verifying that individuals fully disclosed their financial interests. Instead, some universities used informal methods for identifying apparent inconsistencies, such as comparing disclosure forms with those of prior years. They said they relied on investigators to comply voluntarily with conflict-of-interest policies because they believed it was important to have faculty support and maintain collegiality with the investigators. Furthermore, some of the universities emphasized informing faculty about

²²The fifth university was not able to report any information on individual financial relationships.

their financial conflict-of-interest policies, a requirement established in the PHS regulation. To this end, for example, two of the universities had incorporated financial conflict-of-interest education modules into their investigator training.

Research Administration and Financial Relationship Information Kept in Multiple Locations and Formats

The data for overseeing various aspects of investigators' research activities and financial interests were kept in multiple offices, files, and formats within each of the five universities, making it a challenge to ensure that conflicts of interest were appropriately managed and not overlooked. As part of our study, we asked the five universities to provide some basic data on investigators' financial conflicts of interest in clinical research involving human research subjects. All five of the universities had difficulty providing the information requested, and one was not able to provide any of the data. University officials told us it was difficult to respond to our request because information on who received funding to conduct clinical research, their financial disclosures and any management strategies used in the event of a conflict, and the IRB's review of the research protocol was collected in different formats and maintained in separate databases and files in various offices. In general, at these universities, the conflict-of-interest committee or staff to the committee maintained faculty disclosure forms; the grants and contracts office maintained information about who receives funding from government and nongovernment sources, and received reports when there was a financial conflict of interest related to a grant; and the technology transfer office had information about faculty relationships with industry because of its role in helping faculty patent their inventions and license them. While these entities serve distinct purposes, they have information that, collectively, is important to managing investigators' financial conflicts of interest.

Officials at the universities we visited generally acknowledged a need for better coordination among their internal offices that have information about and responsibility for investigators' financial relationships. They also said that a centralized reporting system and integrated database for financial interest information could help ensure that potential conflicts are not overlooked and are monitored. Officials at several of the universities reported they were beginning to develop these linkages.

Because the universities varied in their implementation of the federal financial interest regulation, we observed different practices for reviewing and managing financial conflicts of interest and saw that the universities used different mechanisms for internal coordination and communication.

Officials at some of the universities we visited expressed interest in learning about best practices from HHS and other institutions for identifying and managing financial conflicts of interest in biomedical research, especially as they review and revise their policies.

**Although Not
Required, Universities
Had Policies and
Procedures That
Addressed Aspects of
Institutional Financial
Conflicts of Interest**

While there are no federal regulations or guidelines on institutional financial conflicts of interest or how to manage them, the universities we visited had policies and procedures that addressed aspects of these issues, such as the management of investment funds, technology transfer activities, use of licensing income, and the acceptance of equity in start-up companies. The five universities established a "firewall" between the overall management of university investments and academic affairs, including research activities, by using professional investment managers. University investments in small start-up companies, however, which sometimes occurred as part of technology transfer activities, were more closely tied to research activities. The universities had or were developing policies and practices to mitigate or manage potential institutional financial conflicts of interest in this area, but they varied considerably. One approach was to separate organizationally the technology transfer office from other research activities or to use other internal controls such as special advisory committees to make decisions that otherwise could be influenced by ties to either technology transfer or research activities. Another practice, which all five universities used to varying degrees, was to limit the amount of equity they accepted and the extent of their involvement in managing university-related start-up companies.

**Universities Managed
Institutional Investments
Separately From Academic
Affairs**

The universities we visited established "firewalls" to keep the management of institutional investments separate from academic affairs, including research activities. One university official told us that the organizational barrier this created in large part prevented financial and academic decisions from influencing one another. The five universities used investment managers—either employees or contractors—who were responsible for the university's portfolio and day-to-day investment decisions. The investment managers reported to an investment committee or directly to the university's board of directors. Generally, each university's board of directors had separate committees for investment and for academic affairs that established policies and provided oversight. In addition, these universities, in general, did not devote the university's endowment to investments in university-related start-up companies. At four of the five universities, officials said that most investigators were not aware of institutional investments, suggesting that decisions about these

major university investments were distinct from day-to-day research activities and academic affairs. However, at two of the five universities, general information on how funds are invested, without specific amounts, is available on the Internet. We were unable to readily locate such information at the remaining universities.

Some Universities Tried to Minimize Potential for Institutional Conflicts by Separating the Technology Transfer Office From Academic Affairs

In order to reduce opportunities for institutional financial conflicts of interest, two of the universities organizationally separated the technology transfer office from the research office, locating technology transfer directly under the provost or vice provost, the chief academic officer of the university.²³ Officials at one of these universities said that this arrangement made it easier to manage institutional financial conflicts of interest and that they believed the office of research should not be influenced by technology transfer activities. The other universities located their technology transfer offices under the vice provost for research or vice chancellor for research. One university's justification for locating offices together was that communication was better when these offices were organizationally aligned and that good communication would help prevent financial conflicts of interest from occurring. Officials at another one of these universities gave us an example of an internal control mechanism—establishing an interdisciplinary committee to make an impartial decision about which company is selected to license a product developed by a faculty member—in order to avoid an institutional financial conflict of interest.

²³“Technology transfer office” is a generic title; the universities we visited gave this office various names, such as Office of Cooperative Research and Center for Technology Management. This office encourages the patenting and licensing of discoveries developed by faculty, students, and staff, may help faculty obtain research support from corporate sponsors, and also may be responsible for accepting equity in start-up companies or may work with venture capital companies. At four universities, the technology transfer office's mission was to disseminate research knowledge and provide services to the public. The remaining university stated that its office's mission was enhancing the university's interaction with the private sector and promoting new economic activities within the community.

Universities Placed Limits on Their Equity Holdings and Roles in Start-Up Companies

The five universities we visited had or were developing policies on accepting equity in university-related start-up companies, such as biotechnology companies.²⁴ During the technology transfer phase, universities often accept equity from these companies in return for paying patent and licensing fees.²⁵ The policies at the five universities varied in their stringency. Four restricted the amount of equity they would accept to a fixed proportion ranging from 2 percent to 20 percent. The remaining university specified only that its equity position should not be greater than 49 percent. One university's policy stated that the university generally requires having an equity position in a company when a faculty or staff member develops technology in the course of university employment and assists a business venture in the commercialization of that idea.

Four of the five universities reported that in fiscal year 1999 they spent more in legal fees for technology transfer activities than they were reimbursed through licensing agreements. Their technology transfer offices provide a service to university faculty members and staff in facilitating the transfer of technology to the private sector.²⁶ As one university official said, faculty members should be able to pursue developing products from their research even if they generate little or no profit. Consequently, the universities said that they do not target opportunities for generating profit and that most of their patents and licenses do not yield substantial income.²⁷ The universities do not patent or license all inventions of their faculty and staff, but they do assess whether the technology is worth the investment and assign the rights to the researcher for those they decline to patent or license.

²⁴All five universities have written intellectual property policies specifying the allocation of the derived income for the university, the inventor's school or department, and the inventor. The proportion of the licensing income allocated to the inventor ranged from 25 to 50 percent.

²⁵The cost of patenting and licensing a product averages \$25,000 to \$50,000, and these companies may not have the cash available.

²⁶Written policies on accepting equity in university-related start-ups state that the purpose of accepting equity is to facilitate technology transfer and that this purpose is secondary to the university's primary missions of education, research, and public service.

²⁷Licensing income constitutes a small portion of a university's total research income. Although the five universities ranked among the top universities in licensing income, their licensing incomes ranged from less than 1 percent to nearly 4 percent of their total research income. See The Association of University Technology Managers, Inc., *AUTM Licensing Survey, FY 1999: Full Report* (2000).

Various parties are involved in the decision to accept equity holdings in a university-related start-up. The universities we visited encouraged faculty members and staff to disclose inventions to the technology transfer office. The technology transfer staff review the disclosure to determine both its commercial potential and its ownership. Most universities own intellectual property, such as a patent, if significant university resources were used or if it was developed through research conducted at the university. The technology transfer office then attempts to find a private company to license and underwrite the cost of developing and licensing the product. At the early stage of product development, however, the commercial potential of an invention is often uncertain. If no private company is found to assume the financial risk for developing the product, the university may consider taking an invention through the patenting and licensing process itself and accept equity in payment from the company that will hold the license. At four of the universities, the vice provost or vice chancellor makes the decision to accept equity. At the remaining university, the provost makes the decision. The school or department of the university that employs the inventor also is often involved because, according to all five universities' policies, it receives a portion of the licensing income. It also may provide funds to license and develop the product.

After the decision to take equity, the university's investment managers, who are responsible for the university endowments and investments, then manage the equity shares. University officials told us that once the equity is transferred to these managers, they have virtually no other contact or responsibilities for the equity. However, universities transfer the shares to the investment managers at different times. The technology transfer office at one university holds the equity until the company becomes public, then transfers the equity to the university investment office. Another university has guidelines for placing both individual and university equities in escrow. Other universities transfer the equity after the licensing agreement has been signed. In these cases, university officials said that they are not sure what investment managers do with these holdings—in particular, whether these proprietary holdings are managed differently from other equity holdings.

The universities also restricted their involvement in the management of university-related start-ups because of potential institutional financial conflicts of interest in these ventures. Two universities we visited had written policies that specified the university would not accept representation on a start-up company's board of directors, nor would it exercise voting rights. Another university, however, reserved the right to elect a member to the start-up's board of directors. The member, in this

case, would be required to resign if the company registered with the Securities and Exchange Commission for an initial public offering. The remaining two universities had unofficial policies and are now reexamining the appropriate roles and responsibilities of the university, such as using nonpublic information to manage equity of a university-related start-up and the role of the faculty member who established the start-up in the university's management of the equity.

Current Regulations and Oversight Have Limitations for Promoting Research Integrity and Human Subjects Protection

In our review, we identified limitations with the HHS regulations and oversight of financial conflicts of interest in biomedical research that have implications for promoting the integrity of research and protecting human research subjects. First, no direct link exists between the HHS financial interest regulations and the human subjects protection regulations with regard to the risks to human research subjects posed by investigators' financial conflicts of interest. Second, although the PHS and FDA regulations both address investigators' financial interests, PHS and FDA conduct their reviews of this information at different points in the research process and have different disclosure thresholds for what constitutes a significant financial interest. Third, the universities we visited indicated some confusion about what the PHS regulation specifically required them to report to NIH. NIH and FDA have recently taken steps to improve oversight and monitoring, such as conducting site visits, taking an inventory of institutions' financial conflict-of-interest policies, and providing guidance to reviewers of financial conflict-of-interest information. In addition, HHS has developed draft guidance on financial relationships in clinical research, which is promising. However, this guidance does not provide detailed advice on managing institutional financial conflicts of interest.

No Direct Link Between HHS Financial Interest and Human Subjects Protection Regulations

No direct link exists between the HHS financial interest regulations and the human subjects protection regulations. Such a link would help ensure that IRBs are aware of financial conflicts of interest that might pose risks to study subjects and would help minimize those risks. The PHS and FDA financial interest regulations require disclosure to institutional officials and to sponsors, but there is no mechanism to ensure that the disclosed information reaches IRBs. And although the HHS human subjects protection regulations require IRBs to evaluate research proposals for any foreseeable risks the study might pose to human research subjects, they contain no explicit provision that investigators disclose to IRBs their financial interests. In our review of the five universities, we found that IRBs learned about investigators' financial interests in various ways,

ranging from reviewing financial disclosures directly or receiving reports from the conflict-of-interest committee to informally following up with investigators. Without a direct link between the HHS financial interest and human subjects protection regulations, either institutions are left to develop their own ways to ensure that IRBs have information about financial conflicts of interest or IRBs must seek out this information.

PHS and FDA Financial Interest Regulations Are Not Uniform in Their Timing or Disclosure Thresholds

The timing of the disclosure of financial interests differs between the PHS and FDA regulations. The PHS regulation requires institutions to report to PHS the existence of any financial conflicts of interest before expenditures are made, while FDA reviews investigators' financial interests only when the sponsor submits a marketing application. The PHS regulation requires that investigators receiving NIH funding must disclose to their institutions any "significant financial interests" related to the research. The institution then must determine whether a financial interest constitutes a conflict and, if so, notify NIH that it exists and that it has been managed, reduced, or eliminated. Through the PHS regulation, therefore, institutions and funding agencies have an opportunity before research begins to protect human research subjects from potential harm from investigator conflicts of interest. But while the FDA regulation requires a clinical investigator to disclose financial interests to the sponsor of a trial before beginning to participate, FDA itself is not notified of financial interests that could present a potential conflict of interest until this information is submitted as part of a marketing application, which occurs after the research has been conducted and research subjects have already participated. Although the IRB is responsible for reviewing and minimizing risks to study subjects, the timing of the disclosure of financial interests in the FDA regulation may limit FDA's ability to provide oversight of the process.

The timing of reports to FDA regarding financial interests is geared toward the integrity of research findings. Since the objective of the FDA regulation is ensuring data integrity for the purposes of product review, the regulation focuses on payment arrangements and other financial interests of clinical investigators that could introduce bias into studies. FDA told us that it should be aware of such interests and arrangements as part of its evaluation of marketing applications. An FDA official told us that FDA expected the requirements for disclosure to help deter sponsors from hiring or working with clinical investigators who have significant financial interests that pose a conflict.

PHS and FDA also differ in their threshold amounts for disclosure of financial interests. The PHS threshold—more than \$10,000 in expected

income over 12 months or more than \$10,000 in equity or 5 percent ownership in a company—has not been updated for inflation since the regulation came into effect in 1995. Some have expressed concern that the PHS threshold was too low. For instance, in 1999, members of the NIH Regulatory Burden workgroup stated that the PHS disclosure threshold was too low and could trigger an excessive number of disclosures where there was no conflict that needed to be managed. FDA's thresholds—more than \$25,000 in payments from the sponsor of a clinical study to an investigator or an investigator holding more than \$50,000 in equity in a publicly held company sponsoring the research—are significantly higher than the PHS threshold.

Some Confusion Exists About PHS Reporting Requirements

The PHS regulation requires an institution to report that it has identified a financial conflict of interest related to PHS-funded research and that it has taken steps to manage, reduce, or eliminate it. Nevertheless, we found that officials from the five universities were confused about the conditions under which they needed to report to NIH and what they needed to report. At the universities we visited, we found very few reports to NIH about financial conflicts of interest. This could be because there were few occurrences of significant financial interests involving NIH grants that were deemed conflicts or because we could not determine from the reports whether the universities had followed the reporting requirements. One university operated under the mistaken assumption that it needed to report only financial conflicts of interest that could not be managed; therefore, it did not report them if they had been managed, minimized, or eliminated. At another university, we found a case of clinical research involving human subjects during our file review in which the university established a management strategy for a financial conflict of interest but did not report it to NIH. The university officials told us they had only reported two cases to NIH since the regulation went into effect in 1995, and neither case involved human research subjects.

In some instances, confusion about the requirements and concerns about overreporting may lead to underreporting. Officials from two of the universities told us they were confused about what they needed to report to NIH. One university in our sample did not know whether it was

responsible for reporting a conflict of interest if an investigator had an NIH grant and the conflict was not related to that grant.²⁸

Confusion about reporting requirements also stems from the regulatory silence regarding when financial interests should be viewed as posing a potential conflict. Although the PHS regulation defines a significant financial interest, it allows university officials to determine whether such interests pose conflicts for investigators. Only those financial interests meeting the minimum thresholds that are deemed to be conflicts of interest must be reported. Thus, for example, at one of the universities, a department head deemed that a financial relationship was not a material conflict, even though it was considered a significant financial interest under the PHS regulations.

NIH and FDA Have Taken Steps to Improve Oversight and Monitoring

NIH has taken steps recently to improve compliance with the financial conflict-of-interest regulation by centralizing institutions' reports of conflicts of interest at the Office of Extramural Research (OER), having OER conduct site visits, and taking an inventory of institutions' financial conflict-of-interest policies. NIH is responsible for ensuring that institutions comply with the PHS regulation on financial conflicts of interest. It may do this by reviewing an institution's policies and procedures on financial conflicts of interest, monitoring reports of conflicts, conducting site visits, examining institutions' files, and reviewing actions taken by institutions to manage financial conflicts of interest. Institutions' reports of conflicts are sent to the funding institutes and centers of NIH and are kept with the grant files. Because these reports contain no details about the conflict and its management, NIH program officials have little information to follow up on. NIH is authorized to request more information about conflicts of interest from institutions, but an official at NIH told us that NIH rarely seeks further information. In late 2000, NIH's institutes and centers began providing a copy of grantee institutions' reports of financial conflicts of interest to OER, which maintains summary data on conflicts of interest.

In fiscal year 2000, OER visited 10 institutions receiving NIH funding to assess institutional understanding of NIH policies and requirements, and in

²⁸The PHS regulation requires a significant financial interest to be reported only if it is related to the funding because it "would reasonably appear to be affected by the research for which PHS funding is sought" or if the interest is "in entities whose financial interests would reasonably appear to be affected by the research."

fiscal year 2001, OER visited 8 more institutions.²⁹ Financial conflict of interest was one of many topics addressed. During the visits, the institutions' officials discussed with NIH staff information in financial conflict-of-interest files, including meeting minutes, documents, and correspondence concerning how financial conflicts of interest had been managed, reduced, or eliminated. In its findings and observations on the site visits, NIH noted some of the concerns we have identified. For example, NIH found that some institutions were confused about the definition of a significant financial interest. In addition, some faculty expressed fear that full disclosure of financial interests might result in limiting their institutional salary or adversely affect NIH funding. NIH officials told us that if they discovered a weakness during the visit, they provided guidance and information to help the institution make appropriate improvements.

In January 2001, NIH asked 300 institutions with the largest amount of NIH funding to send it copies of their financial conflict-of-interest policies after officials learned that not all research institutions have an investigator financial conflict-of-interest policy in place. A survey published in 2000 of the 250 medical schools and other research institutions with the highest NIH funding had found that 5 medical schools and 10 other research institutions reported they did not have such a policy.³⁰ As of September 2001, NIH had received policies from 293 of 300 grantee institutions, and all of the top 100 funded institutions had a conflict of interest policy in place. Officials at NIH said they plan to review the policies they have collected to see if they contain all the required elements.

FDA also recently has taken action to improve compliance with its financial interest regulation by providing guidance for FDA reviewers of drug marketing applications. FDA's regulatory role allows it to review the information in investigator financial disclosure reports in marketing applications. If FDA determines that a financial interest of any clinical investigator raises questions about the integrity of the data, FDA may audit the data, ask the applicant to submit further analyses of the data or conduct additional independent studies, or refuse to use the data from that

²⁹OER coordinates this work but supplements its staff with staff from other NIH offices to carry out the work.

³⁰S. Van McCrary and others, "A National Survey of Policies on Disclosure of Conflict of Interest in Biomedical Research," *New England Journal of Medicine*, Vol. 343, No. 22 (2000), pp. 1621-6.

study in support of the product application. Each of FDA's centers responsible for human drugs, biological products, and medical devices determines how it will implement the financial interest regulation.³¹ Until recently, FDA did not provide systematic guidance to its reviewers about evaluating investigator financial disclosure reports. One of FDA's centers has provided guidance by creating a clinical review template for drug marketing application reviewers that includes brief guidance on reviewing financial disclosures.

HHS' Draft Interim Guidance on Financial Conflicts of Interest Is Promising but Limited With Regard to Institutional Conflicts

In December 2000 HHS developed draft guidance entitled "Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider When Dealing With Issues of Financial Interests and Human Subject Protection: Draft Interim Guidance." This guidance drew on information obtained at a conference HHS held in August 2000 on financial conflicts of interest in clinical research³² and comments it received.³³ The document contains guidance for institutions, clinical investigators, and IRBs to assist in their deliberations concerning financial relationships and potential and real conflicts of interest. The document is also intended to facilitate disclosure of such conflicts in consent forms. This document was posted on the OHRP Web site on January 2001 but has not been published in the Federal Register. According to HHS officials, the draft is being revised and will be published as "points for consideration." While it provides promising guidance for identifying and managing individual investigator financial conflicts of interest, it is limited in its discussion of institutional financial conflicts of interest. The draft guidance states that institutions should have policies and procedures on institutional financial conflicts of interest; establish an institutional conflict-of-interest committee to review potential conflicts and their management when considering entering into business agreements; and document and disclose to the IRB institutional financial relationships with a commercial sponsor of a study. But the document does not provide detailed guidance on the appropriate ways of addressing institutional conflicts of interest, particularly institutional relationships with university-related start-up companies.

³¹The responsible centers are the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health.

³²For a transcript of the conference, see <http://ohrp.osophs.dhhs.gov/coi/8-15.htm> and <http://ohrp.osophs.dhhs.gov/coi/8-16.htm>.

³³See <http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finmain.htm>

HHS received 36 comments on its draft guidance from health care professionals, institution officials, and representatives of the patient community, FDA, and academic associations. Some members of the research community expressed concern about the guidance's usefulness and appropriateness. These groups also commented that the academic community had not yet fully discussed institutional financial conflicts of interest and was still grappling with a definition. Some research community members disagreed with giving responsibilities regarding financial conflicts of interest to already overburdened IRBs, which could distract them from their role of protecting human research subjects. Another stated that the draft interim guidance emphasized academic institutions without taking into account the perspective of other types of research centers, such as hospitals and freestanding centers.

After reviewing the draft guidance and comments, the National Human Research Protections Advisory Committee (NHRPAC), an advisory group to HHS, recommended that the Secretary of Health and Human Services move to release the guidance. NHRPAC also recommended that, in the absence of consistent federal regulations, institutions should use the PHS threshold for disclosure of financial interests but that, ultimately, the PHS and FDA thresholds should be harmonized. All research subject to HHS regulations, funded privately or publicly, then would be held to the same standards. Steps toward harmonization, in NHRPAC's view, would include regulatory measures that go beyond the draft interim guidance. In addition, NHRPAC stated that IRBs should not have to collect, analyze, and provide remedies for financial conflicts of interest but should rely on a conflict-of-interest entity (such as a committee or an individual charged with conflict-of-interest review responsibilities) to handle the matters and report formally to the IRB as part of the research application. NHRPAC supported HHS' efforts to identify and define institutional financial conflicts of interest and methods to manage them and suggested that such interests could be disclosed to the institution's conflict-of-interest entity. NHRPAC recommended that specific, detailed information be provided in the informed consent process when an actual conflict of interest has been identified during financial disclosure and, in cases in which a potential conflict is conceivable, to make general information about financial interests available, with more detailed information available upon request. Finally, NHRPAC recommended that institutions audit and monitor compliance with their own institutional policies and procedures and develop and enforce disciplinary standards for violations. The final version of the guidance is scheduled for completion this fall.

Conclusions

The five universities in our study implemented the PHS regulation on individual investigators' financial interests in different ways, and they had or were developing policies and procedures to address aspects of institutional financial conflicts of interest. The universities expressed interest in learning about others' policies and procedures, such as how investigators' financial disclosure information was communicated to IRBs or ways the universities monitored financial conflicts of interest. Having information on the best practices of institutions for dealing with investigator and institutional financial conflicts of interest could help institutions develop policies and procedures that would best meet their needs.

HHS' proposed guidance on financial relationships in clinical research is promising and will help institutions implement the PHS regulation on investigators' financial interests. With some revision, this guidance could link the HHS financial interest regulations with the human subjects protection regulations, making sure that IRBs are aware of financial conflicts of interest to help minimize risks to study subjects. However, the guidance is limited in its treatment of institutional conflicts of interest. As financial relationships between institutions and industry proliferate, the need for guidance in this area increases.

Research institutions are not required to apply their financial conflict-of-interest policies and procedures, as the five we studied did, to both publicly funded and privately funded research. Furthermore, a significant and growing amount of biomedical research is now conducted outside of universities by entities that may not be operating under broad financial conflict-of-interest policies and procedures. Addressing potential financial conflicts of interest in these other settings will be important to ensure the integrity of research and the well-being of human research subjects.

Recommendations for Executive Action

To ensure the integrity of biomedical research and the protection of human research subjects, HHS needs to improve the implementation of its financial interest regulations and its oversight of financial conflicts of interest. Specifically, we recommend that the Secretary of Health and Human Services take the following actions:

- Develop and communicate information on best practices for institutions to consider for identifying and managing investigator and institutional financial conflicts of interest in biomedical research.
- Develop specific guidance or regulations concerning institutional financial conflicts of interest.

Agency Comments

HHS reviewed a draft of this report and provided comments, which are included as appendix III. HHS said that the report gives a useful overview of how some academic research institutions handle financial conflicts of interest and clinical research issues. HHS concurred with our recommendations.

With regard to our recommendation to develop information on best practices, HHS stated that NIH has efforts under way to collect such information by making site visits to institutions and analyzing financial conflict-of-interest policies from institutions. NIH plans to post this information on its Web site. Regarding our recommendation to develop guidance or regulations concerning institutional conflicts of interest, HHS said that NIH's Regulatory Burden Reduction Committee has begun to address institutional conflicts of interest. To the extent that specific policies or guidance on human subjects protection and financial conflict of interest are developed, HHS said it will be coordinated within the Department.

HHS made several specific comments. It noted that financial conflicts of interest occur in the context of all areas of research, not just clinical research. We agree with this assessment, but our report focuses on biomedical research funded or regulated by HHS. HHS suggested that we expand on the rationale for selecting the five universities in our report in order to better explain the institutional variability we observed. We did not add any information because we believe appendix II clearly states our selection criteria and the sample is too small to draw conclusions about how specific characteristics of the universities relate to policy differences.

HHS also noted that one reason NIH typically obtains only limited information about financial conflicts of interest from institutions is that any information NIH has about these matters would be subject to disclosure under the Freedom of Information Act. We agree that financial details disclosed by investigators to NIH potentially are subject to disclosure under the Freedom of Information Act. However, as FDA has recognized in its treatment of such information, the likelihood of such disclosures is slim, and only when necessary to effect a public purpose that outweighs a particular privacy interest. FDA decides such matters on a case-by-case basis and has recognized that, in some cases, there may be legitimate public interests in the financial information of investigators that warrants its disclosure. In its comments, HHS also questioned the purpose for which follow-up information would be gathered. We revised the report to avoid implying that NIH should routinely seek further information and to emphasize instead that NIH already has authority to obtain additional

information on the conflict of interest if it chooses to do so. We believe, however, that there may be instances where NIH may need to know the nature and details of a financial conflict of interest to determine whether it was acted on appropriately.

HHS also stated that concerns remain that the PHS regulation on financial interests does not specifically or adequately address the impact of financial relationships on the interests and welfare of human subjects and added that an IRB may not be the most appropriate body to consider financial conflicts of interest. We have added a discussion about the absence of a link between the HHS financial interest regulations and the human subjects protection regulations. We agree with HHS that an IRB may not be the most appropriate body to review investigators' financial interests and that an IRB can also learn about any risks from conflicts of interest by receiving information from a conflict-of-interest committee or by asking for information directly from investigators.

HHS also provided technical comments, which we incorporated where appropriate.

As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of this letter. We will then send copies to the Secretary of Health and Human Services, the Director of OHRP, the Acting Director of NIH, the Acting Principal Deputy Commissioner of FDA, appropriate congressional committees, and others who are interested. We will also make copies available to others on request.

If you or your staff have any questions, please contact me at (202) 512-7119 or Marcia Crosse at (202) 512-3407. Other major contributors are listed in appendix IV.

Sincerely yours,



Janet Heinrich
Director, Health Care—Public Health Issues

Appendix I: Federal Regulations Pertaining to Financial Interests in Research

Agency, regulation, and effective date	Applicable party	Disclosure requirements	Reporting requirements
Public Health Service (including NIH) Regulation: Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought 42 C.F.R. pt. 50 Subpart F; effective Oct. 1, 1995	Institutions or individuals applying for PHS funding.	Significant financial interests of the investigator (or spouse or dependent child): Significant financial interests are defined as interests that would be affected by research or in entities whose financial interests reasonably appear to be affected by research, including equity interests exceeding \$10,000 or 5 percent ownership in a single entity; salaries, royalties, or other payments (not from applicant institution) expected to total more than \$10,000 in the next year; and patents.	Required financial disclosures of investigators must be provided to the institution by the time the grant application is submitted to PHS. Grant applications to PHS must certify that the institution has implemented a written and enforced administrative process to identify, manage, reduce, or eliminate conflicting interests; that all conflicts have been reported; and that each conflict will be managed, reduced, or eliminated before the expenditure of PHS funds. Investigators must update financial disclosure reports annually or as new interests are obtained.
Food and Drug Administration Regulation: Financial Disclosure by Clinical Investigators 21 C.F.R. pts. 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860; effective Feb. 2, 1999	Applicants who submit marketing applications for human drugs, biological products, or medical devices and submit clinical studies in support of those applications.	Financial interests and arrangements of the investigator: A financial interest or arrangement subject to disclosure includes (1) an arrangement between the sponsor and the investigator (or spouse or dependent child) in which the value of the investigator's compensation could be influenced by the study outcome; (2) significant payments from sponsor to investigator or institution supporting investigator activities that are valued at more than \$25,000 beyond the costs incurred in conducting the study; (3) proprietary interests, including patents, held by the investigator in the product; or (4) significant equity interests in the sponsor of a covered study whose value cannot be readily determined through reference to public prices or valued at more than \$50,000 if a company is a publicly traded corporation. Applicant also must disclose any steps taken to minimize the potential for bias.	Investigators must provide the sponsor with sufficient, accurate financial information needed to allow subsequent disclosure or certification. The applicant must submit, for each investigator who participates in a covered study, either certification that no financial interest or arrangement listed in the regulation exists or disclose the nature of the interest or arrangement to the agency. Certifications and disclosures must accompany marketing application. Investigators must update financial disclosure reports during the course of the study or for 1 year following its completion.

Appendix II: Scope and Methodology

To address our objectives, we reviewed the HHS regulations pertaining to financial interests in biomedical research. In addition, we interviewed officials at the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office for Human Research Protections (OHRP). We also interviewed staff at the American Association of Medical Colleges, the Association of Academic Health Centers, the Association of American Universities, the National Association of College and University Business Officers, the National Bioethics Advisory Commission,¹ and HHS' Office of Inspector General. We also visited five universities that received federal funding for biomedical research in order to understand how they were implementing the HHS financial interest regulations. Our sample selection and data collection are described in the following sections.

Sample Selection

Our sample included public and private academic institutions. Accordingly, this report does not address how financial conflicts of interest in clinical research are managed at hospitals or other research institutions.

Our selection criteria were universities

- that received large amounts of research funding from NIH (top 20 universities);
- had extensive technology transfer activities, according to the Association of University Technology Managers' (AUTM) 1999 licensing survey;²
- had not been extensively scrutinized, audited, or targeted recently for review by NIH's Office of Extramural Research or OHRP; and
- that were located in different geographic areas of the United States.

We visited the following academic institutions: University of California-Los Angeles; University of North Carolina, Chapel Hill; University of Washington, Seattle; Washington University, St. Louis; and Yale University, New Haven.

Given our selection criteria, our sample is biased toward large research universities with complex organizational structures. Medium and small

¹The National Bioethics Advisory Commission was a presidential commission established in 1995 to advise the National Science and Technology Council and other government entities regarding bioethical issues arising from research on human biology and behavior.

²AUTM does not provide specific information on biomedical-related activities.

universities may not necessarily have comparable organizational structures. Consequently, our study results are not generalizable to all universities.

Site Visits

At each of the five universities, we interviewed the following officials: the institution official responsible for research; the head of the conflict-of-interest committee or the institution official responsible for managing conflict-of-interest issues, or both; the chairperson or a member of the institutional review board (IRB), or both; the head of the technology transfer office; and two investigators selected by the university (one receiving NIH funding for research and another receiving private funding).

We reviewed the universities' policies and procedures on financial conflicts of interest, sponsored research, outside professional activities, and equity acquisition. We also reviewed a sample of investigators' financial disclosures for fiscal years 1999 and 2000. Some universities provided copies of these financial disclosures and the university's management plans with the names of investigators and sponsors removed.

To obtain information on the percentage of university clinical investigators with financial interests related to their research, we requested information on the total number of clinical investigators receiving sponsored research funding and the number of those clinical investigators who disclosed financial interests each year from 1995 through 2000. We also requested information on whether the research funding was private or public, the type of financial interests disclosed (for example, income, equity interests, or intellectual property rights), and the type of management strategies employed.

We conducted our work from February through September 2001 in accordance with generally accepted government auditing standards.

Appendix III: Comments From the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

OCT - 1 2001

Ms. Janet Heinrich
Director, Health Care--Public
Health Issues
United States General
Accounting Office
Washington, D.C. 20548


Dear Ms. Heinrich:

Enclosed are the Department's comments on your draft report, "Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest." The comments present the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department also provided extensive technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,


Janet Rehnquist
Inspector General

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

**Comments of the Department of Health and
Human Services on the U.S. General
Accounting Office Draft Report, "Biomedical Research: HHS Direction Needed
to Address Financial Conflicts of Interests."**

Background

The Department's Public Health Service (PHS) has had regulations concerning financial conflicts of interest since 1995 and the Department's Food and Drug Administration (FDA) has had regulations requiring financial disclosure for clinical investigators since 1998. Neither PHS nor FDA requirements are prescriptive regarding the types of financial interests that may be held and neither mentions the role and responsibilities of institutional review boards (IRBs) in this area, nor disclosure of financial arrangements to a research subject via a consent document. Further, both the "Common Rule" which sets out requirements for IRBs at institutions receiving PHS funds, and FDA's equivalent regulations governing IRBs and informed consent, are mostly silent in this area. Accordingly, the Department developed draft interim guidance on financial relationships in clinical research as noted in this report.

General Comments

The General Accounting Office's (GAO) report provides a useful overview of the handling of financial conflicts of interest and clinical research issues at a number of academic medical institutions. The report reviews financial relationships, financial conflicts of interest policies and human subject protections issues. The report helps to elucidate and sharpen a number of issues in this complex area, and will prove useful, particularly to FDA, the Department's National Institutes of Health (NIH), the Department's Office for Human Research Protections (OHRP), and the regulated community.

It would be helpful to list, at the beginning of the report, the purpose of each regulation and a brief summary of what each regulation covers. References to the currently available guidance documents for each regulation would also be helpful. Additionally, in a number of places the term "HHS regulations" is used. This is not accurate and is confusing. It is more useful to cite the specific regulation in more detail (for example, PHS conflicts of interest regulation, the Common Rule, and the FDA financial disclosure regulation). It would be especially helpful to the readers of this report if GAO were to link references to a specific web site. In addition, it might be helpful if a citation to the presentations and discussions of the August 2000 Department-sponsored conference on human subject protections and financial conflicts of interest were referenced. The transcript of the conference is available on OHRP's web site.

For clarity and consistency, it would also be helpful to use the term "financial" conflicts of interest throughout the report. Numerous types of bias can jeopardize judgment and objectivity in research, many of which are nonpecuniary in nature (for example, the desire to validate theories, the desire for publishable results, or the desire to provide desperately ill patients with some kind of intervention option). Because conflicts of interest may be other than financial, it would be helpful to clarify that this report is focused on financial conflicts of interest. Also, the report should indicate that financial conflicts of interest occur in the context of all areas of

research, not just clinical research. While the Department recognizes that this GAO review focused on issues that may affect the protection of human research subjects and how financial conflicts of interest may undermine such protection, it may help other readers for GAO to note that financial conflicts of interest are not an issue exclusively with clinical research.

It is not surprising that there is much diversity in policies and procedures and a need to identify "best practices." The GAO should be commended for the site visits to the five institutions to gather information regarding the implementation of the 1995 PHS regulation on research objectivity. The sections of GAO's draft report on institutional conflicts of interest detail the variability in practices and procedures among the institutions. The financial relationships between academic institutions and for-profit organizations range in size, complexity and involvement. The management of institutional financial conflicts of interest requires tools that reflect this full spectrum of variability, and these tools are best applied at the local level.

It might be helpful to expand on the rationale for selecting the five universities featured in this report. Universities are extremely heterogeneous in many respects, and there may be good reason for the variability in institutional processes and organizational arrangements noted in the report. Perhaps identification of some key characteristics of the selected universities—whether it is public or private; if it has a medical school; or if it is a research-intensive institution—might make it easier to understand the institutional variability that was observed.

The report describes some useful approaches that will be helpful to institutions, IRBs, and clinical investigators. The report relates institutional concerns to both financial conflicts of interest and human subject protection issues. In fact, the report in discussing IRB involvement in the review of financial conflicts of interest (page 15) nicely describes a spectrum of IRB activities.

We believe that one area addressed in the report requires some clarification. The report indicates that the 1995 PHS regulation does not require grantee institutions to submit financial details disclosed by investigators to NIH. But the report does not discuss the rationale *against* requiring submission of investigators' financial information to NIH. This information, if submitted, would enter the Federal Government's system of records and be subject to the Freedom of Information Act (FOIA). There is a substantial risk that disclosure of this information, through FOIA, would violate an investigator's privacy. The NIH has the right to access this information, if needed, which, we believe, is preferable to having NIH routinely receive such information.

Grantee institutions, nonetheless, are required to submit written notification to NIH that financial conflicts of interest disclosed by an investigator are managed, reduced, or eliminated. A notification is kept with an investigator's grant file and provides an additional dimension to the monitoring and oversight of a grant. Absent specific problems or issues with a grant, NIH staff do not routinely follow-up with grantee institutions regarding such notifications. The report discusses follow-up concepts and notes that these actions are rarely taken by NIH staff. The report does not explain what GAO believes such follow-up would entail. If an institution has managed financial conflicts of interest, as required by the 1995 PHS regulation, the need for

routine NIH follow-up is not clear. Nevertheless, there remain concerns that the 1995 regulation, while addressing some issues related to financial conflicts of interest, the regulation does not specifically or adequately address the impact of financial relationships on the interests and welfare of human subjects.

In reviewing research projects, an IRB must assess the risks and benefits of a proposed study. The deliberation may include financial conflicts of interest, but an IRB's risk/benefit assessment is not solely based on reviewing such conflicts. It is unclear if an IRB is the most appropriate review body for consideration of financial conflicts of interest. Certainly, IRBs need to be made aware of and consider such conflicts, but some in the research and other communities suggest that primary responsibility for review of financial conflicts of interest is best done by a review committee with specialized expertise in this area, such as a conflicts of interest committee. Similarly, issues pertaining to protecting human subjects from potential negative impacts of existing financial conflicts of interest are best handled by an IRB. While these committees or processes should interact, steps should be taken to ensure that there is no duplication of effort and that appropriate expertise is brought to bear on both the assessment of financial conflicts of interest as well as human subject protections issues. Many in the research community believe that already overburdened IRBs should not be asked to assume an additional burden of primary responsibility for evaluating financial conflicts of interest. The NIH has placed on their web site examples of ways that institutions might ensure that one of their offices (usually a compliance office) dealing with financial conflicts of interest might interact with their IRB.

GAO Recommendation

To improve the implementation of the HHS conflict-of-interest regulations and HHS' oversight to ensure the integrity of biomedical research findings and the protection of human research subjects, we recommend that the Secretary of Health and Human Services take the following actions:

- Develop and communicate information on best practices for institutions to consider for identifying and managing investigator and institutional financial conflicts of interest in biomedical research.

Department Comment

The Department concurs with this recommendation. The revision of the Department's draft interim guidance should be helpful to institutions, IRBs, and clinical investigators while "best practices" evolve from public and private sector efforts. The NIH has efforts already under way to collect and develop such information for posting on their web pages, based on their proactive site visits and their analysis of financial conflicts of interest policies from the top NIH grantee institutions.

**Appendix III: Comments From the
Department of Health and Human Services**

GAO Recommendation

- Develop specific guidance or regulations concerning institutional conflicts of interest.

Department Comment

The Department concurs with this recommendation, noting that in addition to the Department's draft interim guidance, which touches upon this area, NIH, through the activities of their Regulatory Burden Reduction Committee, chaired by the Deputy Director for Extramural Research, has already begun to address institutional financial conflicts of interest. Furthermore, external groups, such as the Association of American Universities and the American Association of Medical Colleges, are also working on issues related to financial conflicts of interest.

Within the Department, this activity overlaps several domains. The NIH has the primary involvement with institutions in the context of funding extramural research activities under the PHS Act, but other Department operating divisions, (for example, the Centers for Disease and Control and Prevention and FDA) also support clinical research under the PHS Act, and FDA has specific regulatory authorities under the Federal Food, Drug, and Cosmetic Act. The OHRP has the primary responsibility for Department oversight of human subject protections, under regulations set forth in 45 CFR 46, including those associated with financial conflicts of interest, through the institutional assurance process. Matters pertaining to institutional financial conflicts of interest go beyond clinical research and protection of human subjects. These matters are important issues for basic research as well. To the extent that specific policy or guidance on human subject protections and financial conflicts of interest is developed, it will be coordinated within the Department.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-3407

Staff Acknowledgments

In addition to the person named above, Anne Dievler, Bertha Dong, Romy Gelb, Julian Klazkin, and Elizabeth Morrison made important contributions to this report.

Related GAO Products

Human Subjects Research: HHS Takes Steps to Strengthen Protections, but Concerns Remain (GAO-01-775T, May 23, 2001).

VA Research: Protections for Human Subjects Need to Be Strengthened (GAO/HEHS-00-155, Sept. 28, 2000).

NIH Research: Improvements Needed in Monitoring Extramural Grants (GAO/HEHS/AIMD-00-139, May 31, 2000).

NIH Clinical Trials: Various Factors Affect Patient Participation (GAO/HEHS-99-182, Sept. 30, 1999).

Technology Transfer: Reporting Requirements for Federally Sponsored Inventions Need Revision (GAO/RCED-99-242, Aug. 12, 1999).

Technology Transfer: Number and Characteristics of Inventions Licensed by Six Federal Agencies (GAO/RCED-99-173, June 18, 1999).

Medical Records Privacy: Access Needed for Health Research, but Oversight of Privacy Protections Is Limited (GAO/HEHS-99-55, Feb. 24, 1999).

Technology Transfer: Administration of the Bayh-Dole Act by Research Universities (GAO/RCED-98-126, May 7, 1998).

NIH Extramural Clinical Research: Internal Controls Are Key to Safeguarding Phase III Trials Against Misconduct (GAO/HEHS-96-117, July 11, 1996).

Scientific Research: Continued Vigilance Critical to Protecting Human Subjects (GAO/HEHS-96-72, Mar. 8, 1996).

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